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Heme oxygenase/carbon monoxide-biliverdin pathway may be involved in the antinociceptive activity of etoricoxib, a selective COX-2 inhibitor

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Abstract:
The aim of this study was to assess the interaction between the heme oxygenase-1/ biliverdin/carbon monoxide (HO-1/BVD/CO) and cyclooxygenase-2 (COX-2) pathways in the writhing test. Mice were pretreated with 0.1, 1 or 10 mg/kg, *ip* etoricoxib, a selective COX-2 inhibitor, or with one of the following HO-1/BVD/CO pathway modulators: 1, 3 or 9 mg/kg, *sc* ZnPP IX, a specific HO-1 inhibitor, 0.3, 1 or 3 mg/kg, *sc* hemin, a substrate of the HO-1/BVD/CO pathway; or 0.00025, 0.025 or 2.5 μmol/kg, *sc* DMDC, a CO donor. Mice pretreated with etoricoxib or one of the HO-1/BVD/CO pathway modulators received an injection of acetic acid (*ip*) after 30 and 60 min, respectively. Next, the number of writhes was quantified between 0 and 30 min after stimulus injection. In another series of experiments, ineffective doses of etoricoxib were co-administered with hemin or DMDC and an effective dose of etoricoxib with ZnPP IX, followed by an acetic acid injection. Four hours after the acetic acid injection, levels of bilirubin, which is a product of BVD conversion by the BVD reductase enzyme, in the peritoneal lavage were determined. Hemin or DMDC reduced ($p < 0.05$) the number of writhes, but ZnPP IX potentiated ($p < 0.05$) the effect of acetic acid by increasing ($p < 0.05$) the number of writhes. The co-administration of etoricoxib with hemin or DMDC reduced ($p < 0.05$) the number of writhes. However, the analgesic effect of etoricoxib was not observed in the presence of ZnPP IX. Pretreatment with ZnPP IX reduced bilirubin levels, but etoricoxib pretreatment significantly increased the bilirubin concentration in peritoneal exudates. The data obtained from these experiments showed that the HO-1/BVD/CO pathway was activated in the acetic acid-induced abdominal writhing model. The analgesic effect of etoricoxib was at least partially dependent on the participation of the HO-1/BVD/CO pathway.

Key words:
etoricoxib, heme oxygenase, antinociception, mice